Disc-damage Likelihood Scale (DDLS) as a Clinical Indicator of the Presence of a Relative Afferent Pupillary Defect (RAPD)

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Purpose: To evaluate clinical parameters and their relationship to the presence of a relative afferent pupillary defect (RAPD).

Materials and Methods: Retrospective chart review of 672 consecutive patients who presented to the Glaucoma Service at Wills Eye Hospital from January 1 through May 29, 2012. Swinging flashlight method (SFM) was used to test for RAPDs. Records of visual acuity, intraocular pressure (IOP), disc-damage likelihood scale (DDLS), cup/disc (C/D) ratio, visual field mean deviation (MD), optical coherence tomography (OCT), and Heidelberg retinal tomography (HRT) asymmetries were examined. We measured the prevalence of RAPDs as clinical asymmetries increase, calculated cut-off points for clinical asymmetries that optimized sensitivity and specificity in detecting RAPDs, and determined values of clinical asymmetries above which a RAPD always exists.

Results: Upon exclusion, we studied 409 patients, 175 (42.8%) with RAPDs and 234 (57.2%) without. Age, visual acuity, IOP, DDLS, C/D ratio, MD, retina nerve fiber layer thickness by OCT, HRT C/D, and HRT rim area asymmetries all correlated with RAPD status (OCT and HRT parameters did not include enough patients for multivariable analysis or cut-off determination). Multivariable analysis indicated that IOP, DDLS, and MD asymmetries were significantly correlated with RAPD status (P-value < 0.05). Although the optimal cut-off values for the variables retained in the final multivariable model had low sensitivity and moderate specificity, DDLS had the highest specificity of 0.86.

Conclusions: IOP, DDLS, and MD asymmetries had the best correlation with RAPD status, and increased asymmetries in these parameters were associated with higher likelihood of RAPDs. DDLS score had the highest specificity in predicting a RAPD, and DDLS asymmetry scores ≥ 6 identified all cases of RAPDs.

Key Words: glaucoma, relative afferent pupillary defect, disc-damage likelihood scale, cup/disc ratio, asymmetry

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A relative afferent pupillary defect (RAPD) is a sign of asymmetric health of the optic nerve in an individual.[1–5] Presence of a RAPD indicates an unequal ability of the 2 optic nerves to transmit signals to the brain. Etiologies of this phenomenon include pathologies in the retina or the optic nerve, the latter of which may be due to glaucoma. A RAPD has been shown to correlate with estimated retinal ganglion cell loss,[6] retinal nerve fiber layer loss,[1] optic nerve damage,[7] and visual field loss.[8–10] Thus, it can be used to test for asymmetric diseases involving the retina and/or optic nerve.[11]

Studies examining clinical asymmetries related to a RAPD have investigated its prevalence in relationship to the degree of various clinical asymmetries, including: cup/disc (C/D) ratios, the disc-damage likelihood scale (DDLS) score, and mean deviation (MD) of the visual field (VF). Brown et al,[7] in 27 patients with glaucoma, reported a mean difference in C/D ratio of 0.43 (range, 0.2 to 0.6) in patients with a RAPD, versus 0.24 (range, 0.2 to 0.3) in those without a RAPD. The mean difference in visual field (VF) sensitivity was 48.2% (range, 13% to 93%) for the RAPD group and 5.5% (range, 0% to 9.0%) in the non-RAPD group. This implies a greater amount of asymmetry in patients with a RAPD than in those without a RAPD. However, whether there are thresholds of clinical asymmetries that determine whether a RAPD is going to be present or not appears not to have been studied.

We report, here, results of a retrospective study of 448 of 672 consecutive patients followed by the Glaucoma Service at Wills Eye Hospital, in whom RAPDs were routinely tested as a standard part of evaluation of the optic nerve. Our goal was to determine whether relationships exist between the amount of clinical asymmetry and the incidence of positive RAPDs.

MATERIALS AND METHODS

For this study, data from 672 consecutive patients who were followed at the Glaucoma Service of Wills Eye Hospital by a glaucoma specialist (G.L.S.) for definite or suspect glaucoma were collected; the latter group was included because patients without VF loss, but significant asymmetry, may have RAPDs. Identification of a RAPD is especially important in these individuals as it indicates that pathology is present, even in the absence of detectable VF loss.[12] Data collected include demographic information, the presence of a RAPD [assessed by the swinging flashlight method (SFM) or swinging flashlight test (SFT)], visual acuity (VA), intraocular pressure (IOP), DDLS, C/D ratio, and MD. The proportion of patients with RAPDs for each value of asymmetry in VA, IOP, DDLS, C/D ratio, and MD was calculated and the relationships assessed by

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logistic regression and receiver operating characteristic (ROC) analysis.

Inclusion criteria were:

(1) Documented results of RAPD testing.
(2) VF testing, optical coherence tomography (OCT), or Heidelberg retinal tomography (HRT) testing within at most 6 months of documented pupil response testing.

Exclusion criteria were:

(1) Any condition preventing adequate visualization and examination of the pupil or optic nerve (eg, ptosis, dense corneal opacities, or lens opacities), or
(2) patients with only 1 eye or nonresponsive pupils bilaterally, or
(3) active infection/inflammation of the anterior or posterior segments of the eye, or
(4) any intraocular surgical or laser procedure within the previous 4 weeks, or
(5) any other nonglaucoma conditions that may cause a RAPD (ischemic/nonischemic optic neuropathy, macular degeneration, diabetic retinopathy, etc.).

Data regarding RAPD, VA, IOP, C/D ratio, DDLS score, and VF within 6 months of the documented RAPD testing were collected. VA was recorded in LogMAR units and calculations were done using an online converter.[13] "Counting Fingers" or worse were excluded from analysis. C/D ratios and DDLS scores were calculated from clinical documentation with optic disc drawings. DDLS was calculated according to the criteria listed from Figure 1, which was developed by Spaeth and Paulus.[14]

OCT and HRT parameters were also collected if testing occurred within 6 months of the documented RAPD finding and if good quality images were obtained (OCT parameters were included if the images had signal strengths >6; HRT parameters were included if the images had overall quality scores of excellent, very good, or good).

VF testing was done with the Octopus 900 standard automated perimetry (Haag-Streit AG, Koeniz, Switzerland) or Humphrey VF Analyzer (24-2 Swedish Interactive Threshold Algorithm Standard Strategy; Carl Zeiss Meditec Inc., Dublin, CA). Patient data were included only if the VF test was performed within 6 months of the documented RAPD finding and had reliable quality (fixation loss, false-positive, and false-negative errors <15%). The following exclusion criteria were applied: a reliability factor value >15% in either eye, or false positives or false negatives >15% in either eye. The MD asymmetry was calculated by the absolute difference in dB between fellow eyes.

The status of RAPDs was identified by chart review as was the recorded amount of disc or field asymmetry. SFT to determine presence or absence of a RAPD was performed before any consideration of disc or field data, past or present. All patients were examined in the following order: history taking, SFT (performed by G.L.S.), and then assessment of the previously mentioned clinical parameters. Examination results assessed before the history of the SFT were not reviewed for the present examination. The SFT was performed in a dark room (lights off); the patient was instructed to look into the distance; a bright, white light from a transilluminator was directed into the right eye from an angle of around 15 degrees below the visual axis, directly in front of the right eye, about 10 mm in front of the eye, and the right pupil response observed. Next, the light was directed into the left eye, using the same technique, and the left pupil response observed. Subsequently, the light was directed into the right eye for 3 seconds, after which the viewer's gaze was directed to the left and the light directed into the left eye for 3 seconds—at the same distance and angles—and the pupil response observed. This pattern was repeated several times until the image of pupil movement was defined. Pupil response was classified as (1) persistent contraction, (2) contraction followed by slow, partial dilation, (3) contraction followed by rapid dilation with return to the prior pupil size, or (4) immediate dilation. Whenever differences in responses between the 2 eyes were ambiguous, the test was repeated 8 to 10 times until a clear difference was observed or no difference was observed. Neutral density filters were not used, as the purpose of the SFT was to determine if a RAPD was present, not to quantitate its magnitude.

Descriptive statistics were calculated for the RAPD and no RAPD groups for each predictor variable. Differences between groups were assessed with either a t test or Wilcoxon test for continuous variables, and a χ^2 test for discrete variables. Next, a series of univariable logistic regression analyses were performed for each variable to assess the predictive efficacy for detecting RAPDs using odds ratios (representing the odds of having a RAPD for each 1 U increase in the predictor variable), and the C-statistic (which measures the area under the ROC curve) to determine the optimal cut-off point for each variable. A subsequent multivariable model was performed to identify the set of variables that were significant predictors of RAPDs. If >30% of the data were missing for a given variable, it was not included in the multivariable model. Finally, the optimal cut-off point for each significant predictor was assessed by determining the value that maximized sensitivity and specificity.

Statement of Ethics

The study protocol received approval from the Institutional Review Board at Wills Eye Hospital. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS

Of the 672 patients, 224 patients were excluded due to general exclusion criteria, of whom 39 were excluded due to lack of documentation of clinical parameters (C/D ratio, DDLS, and VF results within 6 mo of RAPD documentation). Of the eligible remaining 409, 175 (42.8%) patients had a RAPD and 234 (57.2%) had no RAPD. Figure 2 shows the distribution of disease severity based on VF defects as categorized by Mills et al[15] and divided into Humphrey and Octopus criteria. These results indicate a wide range of disease stages in our study population. In addition, 74% of patients (301) had their VF tested within 3 months of SFM.

Table 1 summarizes descriptive statistics for continuous clinical parameters as well as P-values testing for differences between the RAPD and no RAPD groups. Significant differences between the 2 groups were found for age, VA, IOP, DDLS, C/D ratio, MD, OCT, HRT C/D, and HRT rim area asymmetries (P-values < 0.05). Categorical (demographic) parameters are listed in Table 2; there were no variables with P-values < 0.05. The results of a series of univariable logistic regressions between each clinical parameter and RAPDs are summarized in Table 3. The odds ratio (and 95% confidence interval) for each parameter represents the odds of the presence of a RAPD for each 1 U increase of the predictor variable. The C-statistic represents the area under the ROC curve (with 1.0 indicating perfect predictability and 0.50 indicating

	Narrowest width of rim (rim/disk ratio)				Examples		
DDLS stage	For small disk < 1.50 mm	For average size disk 1.50-2.00 mm	For large disk > 2.00 mm	DDLS stage	1.25 mm optic nerve	1.75 mm optic nerve	2.25 mm optic nerve
1	0.5 or more	0.4 or more	0.3 or more	0a			
2	0.4 to 0.49	0.3 to 0.39	0.2 to 0.39	0b			
3	0.3 to 0.39	0.2 to 0.29	0.1 to 0.19	1			
4	0.2 to 0.29	0.1 to 0.19	Less than 0.1	2			
5	0.1 to 0.19	Less than 0.1	0 for less than 45°	3			
6	Less than 0.1	0 for less than 45°	0 for 46° to 90°	4			
7	0 for less than 45°	0 for 46° to 90°	0 for 91° to 180°	5			
8	0 for 46° to 90°	0 fo 91° to 180°	0 for 181° to 270°	6			
9	0 fo 91° to 180°	0 for 181° to 270°	0 for more than 270°	7a			
10	0 for more than 180°	0 for more than 270°		7b			

FIGURE 1. Disc-damage likelihood scale (DDLS) criteria (Spaeth and Paulus[14]).

predictability no better than chance). All of the statistically significant parameters in Table 1 remained significant with the exception of C/D ratio asymmetry.

Table 4 shows the multivariable analysis of the clinical parameters that were shown to have significant associations with RAPDs in Table 3 (with the exception of OCT and HRT parameters where missing values exceeded 30% of the patient sample). The C-statistic for the overall multivariable model was 0.76. Of the variables retained in the final multivariable model, DDLS had the highest area under curve value by itself (0.69 in Table 3). Optimal cut-off values (maximizing sensitivity and specificity) for IOP, DDLS, and VF parameters are listed in Table 5. The highest sensitivity was MD (0.56) and the highest specificity was DDLS (0.86). The cut-off values above which all patients had RAPDs were summarized in the final column of Table 5. Finally, the sensitivity, specificity, and the cut-off for the combined score were also listed in Table 5.

DISCUSSION

Identifying a RAPD is an inexpensive, accessible, available, and useful way of identifying asymmetric pathology between the 2 optic nerves of the same patient. Clinically, RAPD testing is commonly performed using the SFM. The inherent difficulties of testing for RAPDs this way are well known. Hippus, pupil escape, inadequate light source, nonstandardized conditions of most eye examination rooms, stimulus color, intensity, duration, and other aspects of technique may affect these measurements. There are other established approaches to assessing a RAPD and quantitating the intensity of a RAPD, such as neutral density filters or automated pupillometry devices. These methods quantify the extent of a pupil response but are not necessary to determine whether a response is present. The aim of our study was to: determine whether a RAPD is present by assessing the reactivity of the 2 pupils in comparison with each other; if it was believed that a RAPD was present, determine if the defect correlates with observed asymmetries of clinical parameters; and if there are correlations, which ones were the closest.

Univariable analysis (Table 3), suggests age, VA in LogMAR units, IOP, DDLS, and MD perimetry asymmetries were all significant parameters indicative of a RAPD according to their odds ratios. The difference in age between the 2 groups is of interest in particular, but as RAPD can be a manifestation of more severe glaucoma, it

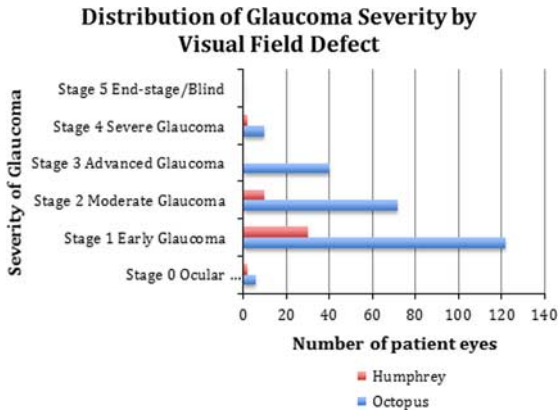

FIGURE 2. Distribution of glaucoma severity by visual field defect categorization was based on the Mills criteria for Humphrey and Octopus. Patients were tested using either Humphrey or Octopus, and criteria were applied accordingly. Humphrey criteria were as follows: stage 0, >0.00 dB; stage 1, −0.01 to −5.00 dB; stage 2, −5.01 to −12.00 dB; stage 3, −12.01 to −20.00 dB; stage 4, ≤20.01 dB; and stage 5, no HVF. Octopus criteria were as follows: stage 0, ≤−0.8 dB; stage 1, −0.7 to +4.4 dB; stage 2, +4.5 to +9.4 dB; stage 3, +9.5 to 15.3 dB; stage 4, +15.4 to +23.1 dB; and stage 5, ≥ +23.2 dB (Mills et al[15]).

is more likely that the result was due to older individuals having more time for disease progression, rather than a direct link. Of the rest of the parameters, they differentiated between patients with a RAPD and without RAPD despite overlap between RAPD and non-RAPD groups; the average values indicating greater asymmetry were consistently higher for individuals with a RAPD (Table 1). However, by multivariable analysis including the above parameters, IOP, DDLS, and MD were the only variables that retained significance. Further, of these 3 factors, DDLS had the highest odds ratio, implying a stronger relationship to the pathology underlying RAPD presentation. These results differ from past studies; in Lankaranian et al's study,[12] MD asymmetry was shown to have a moderate, poorly significant association with RAPDs. Kwon et al[16] demonstrated that while mean asymmetries of IOP were correlated with mean and change in RAPDs over time, 1-time IOP elevations were not correlated with RAPDs; certainly, a single measurement of IOP is not sufficient to indicate the presence of optic nerve damage. These differences in findings may be due to variations in the demographics of the population studied, the sample sizes, and/or the method of RAPD testing; the Lankaranian and Kwon papers studied fewer subjects than the present report, and the latter selected patients on the basis of unilaterally elevated IOP (10 mm Hg higher in one eye than the fellow eye).[14,16]

Another interesting finding of the present study was that, while average C/D ratio asymmetries between patients with a RAPD and patients without a RAPD were statistically different ($P = 0.009$), upon univariate analysis, C/D ratio asymmetry was not correlated with the presence of a RAPD ($P = 0.38$). Brown et al's[7] results showed that the mean difference in C/D ratio and the visual field sensitivity between fellow eye was higher for the RAPD group than that for the non-RAPD group, and in Armaly[17] study, the frequency of C/D ratio asymmetry was also higher among glaucoma patients with a positive RAPD compared with the those without a RAPD. These suggested a relationship

TABLE 2. Association of Relative Afferent Pupillary Defect (RAPD) With Categorical Variables

	RAPD = No, n (%)	RAPD = Yes, n (%)	*P*
Sex*			
Female	153 (65.4)	96 (54.9)	0.031
Male	81 (34.6)	79 (45.1)	
Ethnicity*			
White	186 (79.5)	134 (76.7)	0.477
African American	15 (6.4)	13 (7.4)	
Hispanic	2 (0.9)	0 (0)	
Asian	6 (2.6)	6 (3.4)	
Other	25 (10.7)	22 (12.6)	

*Mantel-Haenszel χ^2 test.

TABLE 1. Association of Relative Afferent Pupillary Defect (RAPD) With Continuous Variables

	RAPD = No			RAPD = Yes			
	n	Mean (SD)	Median (Range)	n	Mean (SD)	Median (Range)	*P*
Age (y)	**234**	**66.6 (16.5)**	**68 (15-98)**	**175**	**70.1 (15.2)**	**72 (17-95)**	**0.028**†
Visual acuity asymmetry (LogMAR)	**232**	**0.11 (0.24)**	**0 (0-1.80)**	**175**	**0.37 (0.61)**	**0.12 (0-2.5)**	**< 0.001**‡
IOP asymmetry (mm Hg)	**230**	**2.24 (3.23)**	**1 (0-24)**	**175**	**3.92 (4.81)**	**2 (0-26)**	**< 0.001**‡
DDLS asymmetry (DDLS units)	**196**	**0.79 (0.89)**	**1 (0-5)**	**149**	**2.00 (2.01)**	**1 (0-9)**	**< 0.001**‡
C/D ratio asymmetry	**91**	**0.16 (0.39)**	**0.1 (0-3)**	**82**	**0.20 (0.28)**	**0.1 (0-2)**	**0.009**‡
MD asymmetry (dB)	**138**	**1.97 (2.36)**	**1.2 (0-17.9)**	**75**	**4.45 (4.29)**	**3.1 (0-15.47)**	**< 0.001**‡
OCT asymmetry (μm)*	**15**	**6.27 (5.15)**	**5 (0-19)**	**9**	**16.55 (14.60)**	**12 (2-50)**	**0.021**‡
HRT C/D asymmetry	**46**	**0.084 (0.10)**	**0.05 (0-0.43)**	**12**	**0.19 (0.16)**	**0.13 (0.04-0.54)**	**0.008**‡
HRT cup shape asymmetry	46	0.067 (0.05)	0.05 (0-0.22)	12	0.16 (0.25)	0.075 (0.01-0.94)	0.175‡
HRT rim area asymmetry (mm^2)	**46**	**0.26 (0.27)**	**00.14 (0.01-1.16)**	**12**	**0.52 (0.41)**	**0.46 (0.09-1.48)**	**0.007**‡
HRT rim volume asymmetry (mm^3)	46	0.14 (0.20)	0.08 (0.00-0.99)	12	0.18 (0.15)	0.14 (0.02-0.55)	0.094‡

Values in bold are statistically significant (*P*-value < 0.05).
LogMAR conversion: counting fingers = 1.9; hand motion = 2.2; light perception = 2.5; no light perception = 2.8.
*OCT asymmetry is average retinal nerve fiber layer thickness.
†Statistical test: *t* test.
‡Kruskal-Wallis test.
C/D ratio indicates cup/disc ratio; DDLS, disc-damage likelihood score; HRT, Heidelberg retinal tomography; IOP, intraocular pressure; MD, mean defect; OCT, optic coherence tomography.

TABLE 3. Univariable Logistic Regression Analysis of Significant Clinical Parameters Predicting Relative Afferent Pupillary Defect (RAPD)

Variable	N	Mean (SD)	Median (Range)	Odds Ratio (95% CI)	*P*	C-Statistic (Area Under the ROC Curve)
Age (y)	**409**	**68.1 (16.0)**	**70 (15-98)**	**1.01 (1.00-1.03)**	**0.0290**	**0.560**
Visual acuity asymmetry (LogMAR)	**407**	**0.22 (0.46)**	**0.079 (0-2.5)**	**5.29 (2.61-10.74)**	**< 0.0001**	**0.65**
IOP asymmetry (mm Hg)	**405**	**2.96 (4.07)**	**2 (0-26)**	**1.12 (1.06-1.19)**	**0.0002**	**0.63**
DDLS asymmetry (DDLS units)	**345**	**1.31 (1.59)**	**1 (0-9)**	**1.91 (1.55-2.35)**	**< 0.0001**	**0.69**
C/D ratio asymmetry ≥ 0.15	173	0.18 (0.34)	0.1 (0-3)	2.30 (1.21-4.34)	0.0110	0.59
MD asymmetry (dB)	**213**	**2.84 (3.38)**	**1.4 (0-17.9)**	**1.27 (1.14-1.41)**	**> 0.0001**	**0.67**
OCT asymmetry (μm)*	24	10.12 (10.78)	7.5 (0-50)	1.18 (0.99-1.41)	0.0660	0.78
HRT C/D asymmetry × 10	**58**	**1.06 (1.18)**	**0.6 (0-5.4)**	**1.97 (1.16-3.36)**	**0.0130**	**0.75**
HRT cup shape asymmetry × 10	58	0.86 (1.27)	0.6 (0-9.4)	1.96 (0.74-5.16)	0.1700	0.63
HRT rim area asymmetry (mm^2)	**58**	**0.31 (0.32)**	**0.19 (0.01-1.48)**	**10.2 (1.44-72.7)**	**0.0200**	**0.75**
HRT rim volume asymmetry (mm^3)	58	0.77 (4.78)	0.1 (0-36.56)	0.92 (0.56-1.51)	0.7400	0.37

Values in bold are statistically significant (*P*-value < 0.05).
Note: LogMAR conversion: counting fingers = 1.9; hand motion = 2.2; light perception = 2.5; no light perception = 2.8.
*OCT asymmetry is average retinal nerve fiber layer thickness.
C/D ratio indicates cup/disc ratio; CI, confidence interval; DDLS, disc-damage likelihood score; HRT, Heidelberg retinal tomography; IOP, intraocular pressure; MD, mean defect; OCT, optic coherence tomography.

between C/D ratio and RAPD. However, Brown had also reported the presence of a RAPD correlated with visual field asymmetry, but not with C/D ratio asymmetry. Other studies have suggested that the relationship between DDLS and VF loss is closer than that between C/D and field loss.[15,18] Our findings were, therefore, consistent with these studies. Although C/D ratios are widely used as a clinical indicator of optic nerve damage, C/D ratios do not take into account the size of the optic disc nor the eccentricity of the cup of the optic nerve. Therefore, in some cases, C/D ratios may not accurately reflect ocular pathology that would cause a RAPD.

In addition to the above parameters, HRT C/D asymmetry and HRT rim area asymmetry were statistically correlated with the presence of a RAPD ($P < 0.05$, C-statistic 0.75), and were significantly different regarding average asymmetry between patients with a RAPD and without RAPD. However, less than one third of patients had HRT testing within 6 months of RAPD record, so we did not include these parameters in the multivariable analysis. In addition, asymmetry of average retinal nerve fiber layer thickness for OCT was found to have the highest C-statistic out of all the parameters, but this correlation was only trending toward statistical significance ($P = 0.066$). In addition, average HRT rim area and C/D asymmetries were statistically different in patients with RAPD and those without. Both HRT and OCT data were assumed to be independent of other parameters during our analysis. Further study regarding the correlation between RAPDs and HRT or OCT may be warranted as objective parameters to determine degree of significance and independence.

TABLE 4. Multivariable Logistic Regression Analysis of Significant Clinical Parameters Predicting Relative Afferent Pupillary Defect (RAPD)

Variable	Odds Ratio	*P*	C-Statistic (Area Under the ROC Curve)
Age (y)	0.99 (0.97-1.01)	0.300	0.76
Visual acuity asymmetry (in LogMAR units)	5.66 (0.69-46.7)	0.110	
IOP asymmetry (mm Hg)	1.12 (1.01-1.24)	**0.037**	
DDLS asymmetry (DDLS units)	1.42 (1.06-1.91)	**0.019**	
MD asymmetry (dB)	1.17 (1.04-1.32)	**0.011**	

Values in bold are statistically significant (*P*-value < 0.05).
n = 179 (RAPD = yes = 64).
DDLS indicates disc-damage likelihood score; IOP, intraocular pressure; MD, mean defect.

Regarding IOP and MD, there was neither a level of asymmetry below which no one presented with a RAPD, nor a value above which all patients had a RAPD. No threshold could be established on the basis of the results of visual field testing; the greatest degree of field asymmetry noted (with a difference of 17.9 dB between the 2 eyes) was not associated with a RAPD. A similar lack of threshold relationship between IOP and the presence of a RAPD was also observed. Thus, while a greater amount of asymmetry increases the likelihood that a RAPD will be present, there is no threshold of asymmetric values of VF or IOP above which one can be certain that a RAPD will be present or below which a RAPD will certainly be absent. In contrast, there is a stronger relationship between the severity of the DDLS score and the presence of a RAPD in comparison with these other parameters; whereas DDLS also had no value below which RAPD is always absent, all patients with asymmetry of > 5 U had a RAPD. When we applied an optimal cut-off point for each of IOP, DDLS, and MD parameters, defined as the point that minimizes the distances from both the sensitivity and specificity of 100%, none of the cut-off values were sensitive in predicting a RAPD. Regarding specificity, the DDLS score performed best. The sensitivities and specificities may be improved with larger sample sizes, but due to the low number of patients that meet these thresholds, no concrete cut-off value could be determined.

An attempt to identify the classification rule for RAPDs, based on variables with cut-off values, was made using recursive partitioning with the conditional inference method as implemented in the R package "party" as

TABLE 5. Optimal Cut-off Points for Significant Clinical Variables in Relation to Relative Afferent Pupillary Defect (RAPD)

Variable	Cut-off Value	Sensitivity	Specificity	Value Above Which All Were RAPD Positive
IOP asymmetry (mm Hg)	2	0.4942	0.7336	24 (2 patients)
DDLS asymmetry (DDLS units)	2	0.4765	0.8622	5 (9 patients)
MD asymmetry (dB)	2.9	0.5616	0.7813	0*
Combined score†	−0.84	0.7031	0.6870	2.39 (6 patients)

The cutpoints for each asymmetry variable were determined using the criteria that the sensitivity and specificity of the cutpoint would be the smallest distance from the perfect test (with sensitivity and specificity of 100%).

*Highest asymmetry was 17.9 dB, with no RAPD.

†Combined score = $-1.72 + 0.1664 \times$ MD_asymmetry + $0.0998 \times$ IOP_asymmetry + $0.3293 \times$ DDLS_asymmetry.

DDLS indicates disc-damage likelihood score; IOP, intraocular pressure; MD, mean defect.

described by Hothorn et al,[19] but the algorithm only split on MD asymmetry without incorporating other variables. Predicted log odds were taken from the logistic regression model parameters in Table 5 to calculate a combined score that can give an optimal cut-off point above which all patients have a RAPD. The formula is as follows:

$$\text{Combined score} = -1.72 + 0.1664 \times \text{MD asymmetry} + 0.0998 \times \text{IOP asymmetry} + 0.3293 \times \text{DDLS asymmetry}$$

As Table 5 shows, the cut-off value was placed at −0.84, above which the result is positive for a RAPD. This had weak to moderate sensitivity and specificity of 0.70 and 0.69; as such, this formula is clinically no more beneficial than DDLS asymmetry alone.

There are certain strengths to this study. In this study, SFT was performed in all cases before review of the previous record and before evaluation of the visual field or optic discs. Therefore, the examiner was not biased by knowing the degree of asymmetry before testing for a RAPD. Further, the mere presence of glaucoma does not mean a RAPD will be present, nor the absence of glaucoma indicates that a RAPD will not be present. Thus, because patients with glaucoma may or may not have a RAPD, knowledge of the patient's status regarding the presence or absence of glaucoma should not bias testing for a RAPD.

Second, the retrospective nature of this study actually represents one of its strengths. Because the population study was one in which a standardized method of testing for RAPDs had been utilized routinely, and SFM had not been performed to determine the relationship between the incidence of RAPDs and the level of clinical asymmetries, these cases provide a remarkably unbiased answer to our study question.

There are significant limitations to our study. First, the study population recruited from our referral practice consists predominately of persons of European ethnicity. The tertiary nature of the practice suggests that this population is not likely to be representative of all patients with glaucoma. Second, not all the tested parameters are in ubiquitous use. Third, it is possible that some patients' observed VFs were not representative of their actual VF at the time of the pupillary testing, as changes may have occurred between the time the VF was performed and the time the patient was examined. We believe this is not likely to be a concern in our study, because 74% had their VF performed within 3 months of the time of the pupil testing. Similarly, 16 of 24 patients had their OCTs performed within 3 months of pupil testing, and 53 of 58 patients had their HRT parameters measured within 3 months of the time of pupil testing. In addition, most patients in this study had early glaucoma, based on the distribution of glaucoma severity by VF defect.[15] We believe, also, the patients included in our study were stable during the intervals of VF testing. Fourth, even though all of the RAPD assessments were evaluated by 1 expert glaucoma specialist (G.L.S.), there may have been intraobserver variability and nondifferential misclassification in determination and documentation, which may introduce error and affect the interpretation of results. Fifth, histories were taken before SFM, which may have introduced observer bias, particularly in patients that were known to the clinician.

Finally, the presence of a patient with a MD asymmetry of 17.9 dB, but no RAPD, raises concerns that some factors may have affected the accuracy of VF testing. Although it is possible that patients can have very asymmetric VFs without RAPDs, it is also possible that the patient did not truly have 17.9 dB of difference, for reasons including errors in data input. Future investigations with larger sample sizes may address the wide clinical variability in parameters measured in this study, as well as provide a more concrete cut-off value for asymmetries that would predict presence or absence of RAPD. Although the number of patients with HRT and OCT data was not large enough to yield generalizable conclusions, those that did have these parameters showed that HRT C/D and rim area asymmetries may have statistically strong correlations with the occurrence of RAPD; further exploration is warranted to assess these relationships.

The amount of asymmetry in IOP, DDLS, and MD of Humphrey and Octopus visual fields all strongly influence the likelihood of the presence of a RAPD; increasing asymmetries in these parameters led to increasing incidences of RAPD. The strongest correlation between the finding and the presence of a RAPD was for the DDLS.

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